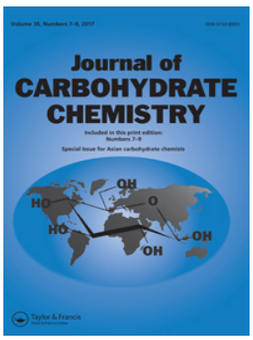

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Modifications at the 6-*O*-position of 1-deoxynojirimycin: facile and efficient synthesis of 6-*O*-alkylated-*N*-octyl-1-deoxynojirimycin derivatives

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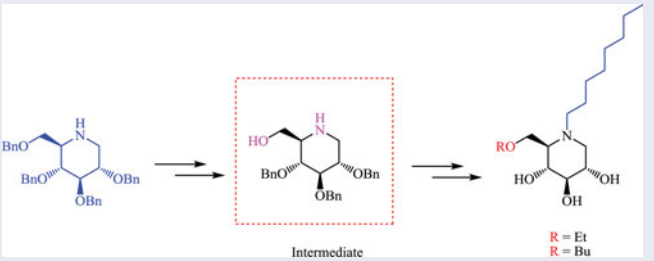
ABSTRACT

A straightforward synthesis of *N*-alkylated 1-deoxynojirimycin derivatives modified at the 6-*O*-position has been described. The key intermediate in the synthesis of target compounds was 2,3,4-tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol, which was prepared from 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol. Optimal conditions have been established for the synthesis of the key intermediate by varying reaction parameters. Reductive amination and subsequent alkylation of the 6-*O*-position followed by hydrogenolysis were the main reaction steps, which gave target compounds 6-*O*-ethyl-*N*-octyl-1,5-dideoxy-1,5-imino-D-glucitol and 6-*O*-butyl-*N*-octyl-1,5-dideoxy-1,5-imino-D-glucitol. This synthetic route is flexible and can be useful for the synthesis of other lipophilic iminosugar derivatives.

GRAPHICAL ABSTRACT



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Gaucher disease; glycosylceramide synthase; 1-deoxynojirimycin; *N*-alkylation; total synthesis

Introduction

Iminosugars, also known as azasugars, are sugar mimics having an endocyclic nitrogen atom instead of an oxygen atom and are potent inhibitors of several types of sugar processing enzymes, such as glycosidases and glycocyltransferases.[1] Thus, they have therapeutic potentials against many diseases such as diabetes, viral infection, Gaucher disease and tumor metastasis.[2–5] The archetypal 1-deoxynojirimycin

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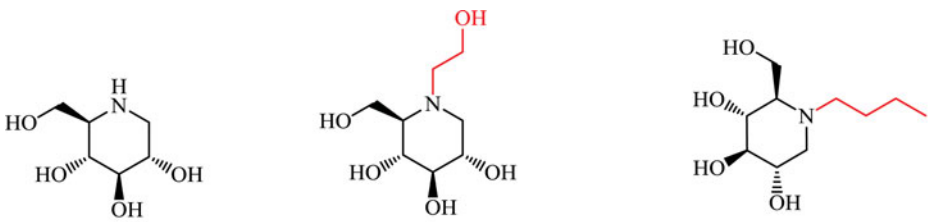


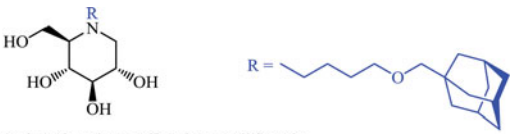
Figure 1. Structures of several *N*-alkyltaed-1-deoxynojirimycin derivatives as drugs approved for clinical usage.

1 and miglitol **2** (Figure 1), which inhibit enzymes including sucrase and maltase and have been approved as antidiabetic drugs, are representatives in this regard.[6] Among these polyhydroxylated alkaloids, *N*-alkylated-1-deoxynojimycin derivatives are especially important due to their usage for treating lysosomal glycosphingolipidose disorders. For example, Zavesca **3**, i.e., *N*-butyl-1-deoxynojirimycin (NB-DNJ) also commonly known as Miglustat, is an oral drug for the treatment of Gaucher disease (Figure 1).[7–9]

Glucocerebrosidase (E.C. 3.2.1.45) is an enzyme that hydrolyzes glucocerebroside (GlcCer) into glucose and ceramide, while Gaucher disease is caused by the defective activity of glucocerebrosidase and thus characterized by the accumulation of GlcCer in tissues.[10] Enlarged organs, bone lesions, obesity, abnormalities of blood glucose level, insulin resistance, and central nervous system impairment are linked with lysosomal storage disorders.[11] Enzyme replacement therapy (ERT) is used for the treatment of Gaucher disease, in which recombinant glucocerebrosidase is injected intravenously. Although this method towards Gaucher disease is direct and effective, its high cost has encouraged the discovery of small molecule-based pharmacological chaperons.[12] A new approach, namely substrate reduction therapy (SRT), could reduce the biosynthesis of GlcCer by partial inhibition of glycosylceramide synthase GCS (E.C. 2.4.1.80).[13]

Zavesca **3** inhibits GCS in patients who are not compatible with ERT. It also targets intestinal sucrose and maltase.[10,14] Wennekes et al.[15,16] reported the synthesis of lipophilic 1-deoxynojirimycin derivatives based on the lead compound *N*-[5-(adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin (AMP-DNM) **4** (Figure 2), which was proved to be 100 times more potent against human GCS than **3**. Derivatives having *N*-methyl modification and 6-*O*-modification with adamantane-1-yl-methoxy moiety exhibited more selectivity towards glucocerebrosidase.

The hydroxy groups in *N*-alkylated-1-deoxynojirimycin derivatives are crucial for the enzyme inhibition as described by van den Berg et al.[17] However, it was found that the hydroxy group at the C6-position was not as important as that at the C2- and C3-positions and is thus more amenable for further modification.



N-[5-(adamantane-1-yl-methoxy)-pentyl]-1-deoxynojirimycin

AMP-DNM

4

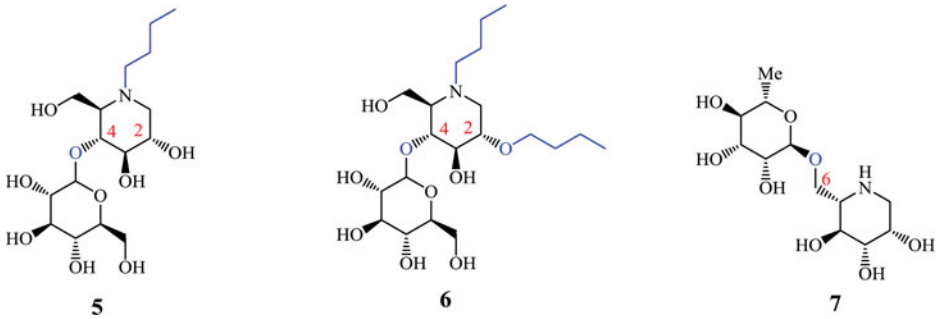
Figure 2. Structure of lipophilic AMP-DNM **4**.

Glycosylation of 1-deoxynojirimycin derivatives with a 2,3,4,6-tetra-*O*-acetyl-a-D-glucopyranosyl moiety in quest for better GCS inhibitors have been reported by Boucheron et al.[18] Selective alkylation at the 2-*O*-position of iminosugars and glycosylation with a sugar moiety at the 4-*O*-position gave iminodisaccharides such as **5** and **6** (Figure 3), which showed satisfactory GCS inhibition results. Similarly, 6-*O*-α-L-rhamnopyranosyl-DMJ **7** (Rha-DMJ), which is a glycoside of DMJ, was synthesized efficiently with modification at the 6-*O*-position (Figure 3).[19]

Inspired by the excellent results derived from selective modification of the alkyl chains in the iminosugar scaffold, herein we report the synthesis of 6-*O*-alkylated-*N*-octyl-1-deoxynojirimycin derivatives commencing from 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol. The design of these new compounds was to alkylate both the nitrogen atom and the 6-*O*-position of iminosugar, which could potentially allow the discovery of new potent glucocerebrosidase inhibitors and pharmacological chaperones for Gaucher disease treatment. The key steps for the target compounds synthesis were *N*- and 6-*O*-alkylations followed by hydrogenolytic deprotection.

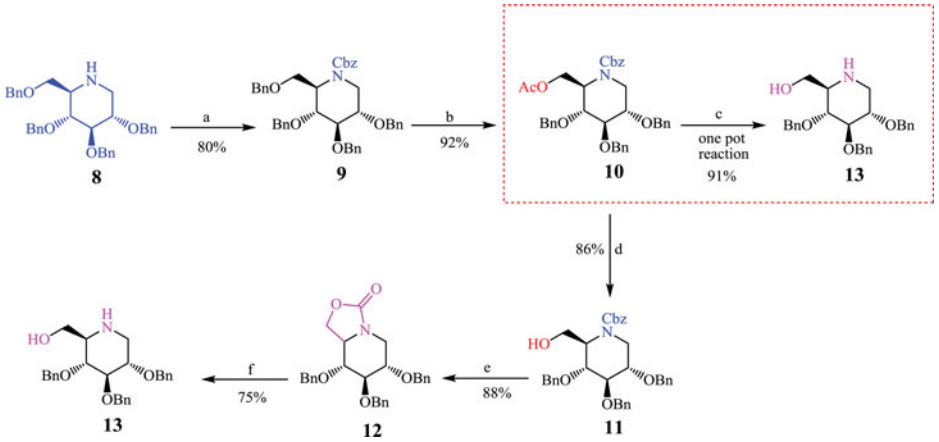
Results and discussion

A successful strategy was developed for gluco-configured 6-*O*-alkylated-*N*-octyl-1-deoxynojirimycin derivative synthesis (Scheme 1), starting from 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol **8**, which was prepared according to the literature.[20] Benzyloxycarbonyl (Cbz) protection of the free amino group in **8** was carried out by reacting with benzylchloroformate to form 2,3,4,6-tetra-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol **9** in a good yield



5 **6** **7**

Figure 3. Structures of lipophilic deoxynojirimycin derivatives with modifications at different positions.



Scheme 1. Reagents and conditions: (a) benzyl chloroformate, aq. $NaHCO_3$, 1,4-dioxane, rt, 18 h; (b) $ZnCl_2$, Ac_2O, AcOH, rt, 18 h; (c) see Table 1; (d) cat. NaOMe, MeOH, rt, 2 h; (e) conc. NaOMe, MeOH, rt, 6 h; (f) 50% KOH, MeOH, 80°C, 20 h.

(80%). The benzyl ether at the primary 6-*O*-position in **9** was selectively cleaved and acylated in situ on treatment with $ZnCl_2$ and Ac_2O/AcOH to give 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol **10** in a 92% yield. Stepwise acylations of the *N*- and 6-*O*-positions were important because direct deprotection and acetylation of the 6-*O*-position in **8** would also acetylate the nitrogen atom, which would be very difficult to deprotect. For example, *N*-acyl group can only be removed under harsh basic conditions or by peroxide in water with utmost precaution.[21] An *N*-acylated iminosugar derivative was deprotected with BH_3-THF and NaOH-H_2O_2 to obtain the free amine, but this procedure afforded only a 31% yield.[22]

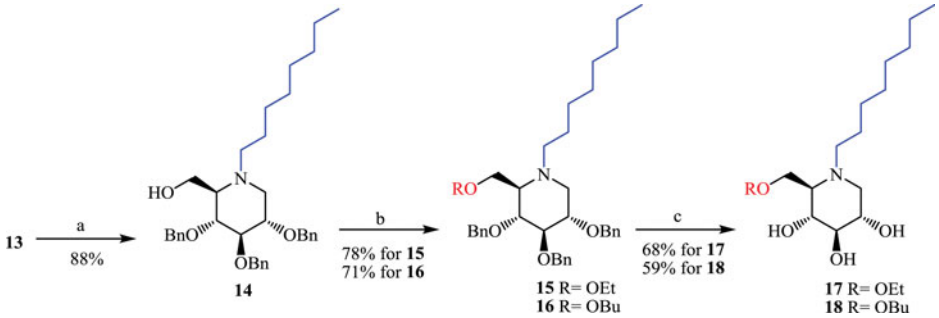
Zemplen deacetylation of compound **10** was carried out by using catalytic amount of sodium methoxide (NaOMe) in MeOH at room temperature for 2 h to give 2,3,4-tri-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol **11** in an 86% yield. Acid resin was used to quench the reaction mixture. It was noted that stronger basic conditions, e.g. using more concentrated NaOMe, converted **11** into cyclic carbamate **12** in an 88% yield. One of the spectroscopic proofs for the product was that the ^{1}H NMR signal of the Cbz group in **11** (at $\delta = 5.17$ ppm) disappeared upon conversion to **12**. Cyclic carbamate **12** needed to be treated with concentrated potassium hydroxide solution (50%) in MeOH under refluxing conditions to obtain 2,3,4-tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol **13** in a 75% yield (Scheme 1).

To optimize the synthesis of **13**, we probed the impacts of different bases on the deacylation of **10** in different solvents. As shown in Table 1, the reaction went smoothly in the presence NaOH (entry 1) in MeOH, which gave a 77% yield of **13** after 6 h of refluxing. Delightfully, when NaOH was changed to KOH (entry 2, Table 1) and solvent was switched to EtOH, the reaction gave the target product in a 91% yield. Use of EtOH and NaOH under refluxing condition also gave an improved

Table 1. Optimization of formation of **13** in one pot reaction by **10**.

Entry	Base[a]	Solvent[b]	Time(h)	Yield[c] (%)
1	NaOH	MeOH	6	77
2	KOH	EtOH	12	91
3	NaOH	EtOH	12	87

Conditions:
[a]50% solution in water (20 mL),
[b]refluxed for 6–12 h in specified solvent (20 mL);
[c]isolated yield.



Scheme 2. Reagents and conditions: (a) n-octanal, $NaCNBH_3$, AcOH, MeOH, 80°C, 12 h; (b) ethyl iodide (for **15**) or butyl bromide (for **16**), NaH, DMF, 0°C to rt, 6 h; (c) Pd/C, H_2 (1 atm), MeOH, conc. HCl (1 mL), 24–48 h, rt.

yield (87%, entry 3, Table 1). It was thus established that the optimal yield of **13** was obtained with the use of KOH in EtOH under refluxing condition for 12 h.

Next, intermediate **13** was *N*-alkylated with n-octanal successfully through reductive amination to afford 2,3,4-tri-*O*-benzyl-*N*-octyl-1,5-dideoxy-1,5-imino-D-glucitol **14** in an 88% yield, as shown in Scheme 2. Thereafterm the free hydroxy group in **14** was alkylated using ethyl iodide or butyl bromide in the presence of sodium hydride to result in 6-*O*-alkylated iminosugar derivatives 6-*O*-ethyl-2,3,4-tri-*O*-benzyl-*N*-Octyl-1,5-dideoxy-1,5-imino-D-glucitol **15** (78%) and 6-*O*-butyl-2,3,4-tri-*O*-benzyl-*N*-octyl-1,5-dideoxy-1,5-imino-D-glucitol **16** (71%), respectively. Deprotection of **15** and **16** was carried out under H_2 (1 atm) using Pd/C as the catalyst to obtain 6-*O*-ethyl-*N*-octyl-1,5-dideoxy-1,5-imino-D-glucitol **17** (68%) and 6-*O*-butyl-*N*-octyl-1,5-dideoxy-1,5-imino-D-glucitol **18** (59%), respectively, as shown in Scheme 2.

Conclusion

In summary, we have synthesized two 6-*O*-alkylated-*N*-octyl-1-deoxynojirimycin derivatives starting from 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol **8**. The key intermediate 2,3,4-tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol **13** was synthesized successfully form **10** by a one-pot reaction. The main steps involved in the target compound synthesis were *N*-alkylation, subsequent modification at the 6-*O*-position, and hydrogenolytic deprotection. The synthetic route developed herein is facile and efficient as various compounds formed during the process can

be used for additional modification and for future research. In short, the target compounds **17** and **18** were synthesized for the first time and may find therapeutic applications.

Experimental

General methods

All commercially available chemicals were used without purification. Solvents were dried prior to use according to standard protocols. Reactions were performed at ambient temperature unless stated otherwise. Moisture sensitive reactions were carried out under an argon environment. Reaction progression was monitored using thin layer chromatography over 0.2 mm thick silica coated plates. Spots were detected under UV-light at wavelength (λ) 254 nm. Iminosugars detection was accomplished via exposure to Iodine vapors. Flash chromatography was performed on silica gel 230–430 mesh (Merck). Melting points were recorded in open glass capillaries and were not corrected. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$/MeOD on broker Avance III 500 MHz spectrometer. Chemical shifts are given using tetramethysilane ($\delta_{TMS} = 0$ ppm) as an internal standard.

Synthesis of 2,3,4,6-tetra-O-benzyl-N-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol (9)

To a solution of 2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol **8** (3 g, 5.7 mmol) in 1,4-dioxane (55 mL) at room temperature, aqueous solution of 10% sodium bicarbonate (20 mL) was added. Next benzyl chloroformate (Cbz-Cl, 1.2 mL, 8.55 mmol) was slowly added to this cloudy solution and the reaction was stirred for 18 hours at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate EA (3 × 200 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification via flash chromatography using gradient elution (SiO_2, petroleum ether/ethyl acetate 5:1, v/v) gave **9** (3 g, 80%) as colorless oil. Yield 80%, colorless oil, $R_f = 0.92$ (petroleum ether/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.38 (m, 25H), 5.14 (d, $J = 12.3$ Hz, 1H), 5.10 (d, $J = 12.3$ Hz,1H), 4.61–4.80 (m, 8H), 4.35 (dd, $J = 9$, 3 Hz, 1H), 4.09–4.27 (m, 2H), 3.92 (t, $J = 6.3$ Hz, 1H), 3.71–3.83 (m, 1H), 3.67 (m, 2H), 3.35 (dd, $J = 14.4$, 3.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.90, 137.23, 137.10, 135.69, 127.40, 127.03, 126.92, 126.79, 126.58, 80.74, 77.13, 73.16, 72.22, 72.01, 71.95, 69.67, 67.43, 66.32, 54.69, 40.26. HRMS (ESI): m/z calculated 658.3090 for $[C_{42}H_{43}NO_6 + H]^+$, found 658.3126.

Synthesis of 6-O-acetyl-2,3,4-tri-O-benzyl-N-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol (10)

$ZnCl_2$ (6.2 g, 45.6 mmol) was added to the dry solution of 2,3,4,6-tetra-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol **9** (3 g, 4.56 mmol) in a

mixture of AcOH (18 mL) and Ac_2O (36 mL) and stirred for 20 hours. Reaction was quenched with water (20 mL) after completion of the reaction (as indicated by TLC) and stirred for another 30 minutes. The reaction mixture was poured slowly into the stirring solution of concentrated Na_2CO_3 (200 mL) and extracted with DCM (3 × 100 mL). Combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography using gradient elution (SiO_2, petroleum ether/ethyl acetate 4:1, v/v) afforded **10** (2.58 g, 92%) as colorless oil. Yield 92%, colorless oil, $R_f = 0.43$ (petroleum ether/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.41 (m, 20H), 5.20 (m, 2H), 4.63–4.79 (m, 5H), 4.53–4.55 (m, 2H), 4.37–4.41(m, 1H), 4.27–4.30 (m, 2H), 3.82 (t, $J = 10$Hz, 1H), 3.70–3.73 (m, 2H), 3.35 (d, $J = 15$ Hz,1H), 2.06 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.67, 155.10, 137.05, 136.90, 135.60, 127.53, 127.45, 127.06, 126.94, 126.81, 126.68, 78.46, 75.90, 72.56, 71.81; 71.60, 69.65, 66.47, 61.19, 53.14, 38.97, 19.80. HRMS (ESI): m/z calculated 610.2727 for $[C_{37}H_{39}NO_7 + H]^+$, found 610.2768.

Synthesis of 2,3,4-tri-O-benzyl-N-benzyloxycarbonyl-1,5-dideoxy-1, 5-imino-D-glucitol (11)

Catalytic amount of sodium methoxide (0.025 M) was added into the dry solution of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol **10** (250 mg, 0.41 mmol) in MeOH (3.6 mL) under argon environment at 0°C and mixture was stirred for 2 hours at room temperature. After indicated time, the reaction was quenched by adding Amberlyte resin (H^+) until neutral pH was obtained. The mixture was filtered off and filtrate was concentrated. The residue was purified by flash chromatography using gradient elution (SiO_2, petroleum ether/ethyl acetate 1:1, v/v) to obtain **11** as colorless oil which solidified at room temperature as white solid (200 mg, 86%). Yield: 86%, white solid, mp: 188–191°C, $R_f = 0.68$ (petroleum ether/ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20–7.38 (m, 20H), 5.05–5.20 (m, 2H), 4.50 (d, $J = 11.8$ Hz, 1H), 4.68 (m, 5H), 3.9 (m, 3H), 3.56–3.70 (m, 3H), 3.64 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.90, 137.23, 137.15,135.69, 127.40, 127.03, 126.92, 126.79, 126.58, 125.50, 80.7, 77.13, 73.16, 72.22, 72.01, 69.7, 67.43, 66.32, 54.69, 40.26. HRMS (ESI): m/z calculated 568.2621 for $[C_{35}H_{37}NO_6 + H]^+$, found 568.2655.

Synthesis of 2,3,4-tri-O-benzyl-1,5-dideoxy-1,5-imino-D-glucitol-N-cyclic carbamate (12)

Sodium methoxide (285 mg, 5.3 mmol) was added in portions to the dry solution of 2,3,4-tri-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol **11** (300 mg, 0.53 mmol) in MeOH and stirred the reaction mixture under an argon environment at room temperature for 6 hours. Completion of the reaction was indicated by TLC and the solvent was removed under reduced pressure. Water was added and extractions were made with EA (3 × 50 mL). Combined organic layers were washed with aqueous $NaHCO_3$ (50 mL) and brine (50 mL). Organic layers were

dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography using gradient elution (SiO_2, petroleum ether/ethyl acetate 2:1, v/v) to afford **12** (214 mg, 88%) as white solid. Yield 88%, white solid, mp: 95–100°C, $R_f = 0.47$ (petroleum ether/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.44 (m, 15H), 5.08 (d, $J = 10.85$ Hz, 1H), 4.98 (d, $J = 11.5$ Hz, 1H), 4.91 (d, $J = 10.85$ Hz, 1H), 4.75–4.80 (m, 2H), 4.69 (d, $J = 11.5$ Hz, 1H), 4.32 (t, $J = 8.85$ Hz, 1H), 4.12 (dd, $J = 5.6, 7.75$ Hz, 1H), 3.80–3.82 (m, 1H), 3.60–3.79 (m, 3H), 3.39 (t, $J = 9.05$ Hz, 1H), 2.84 (dd, $J = 10.05, 3.2$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.73, 137.33, 136.76, 127.74, 127.64, 127.55, 127.37, 127.30, 127.04, 126.91, 84.71, 78.88, 74.97, 74.15, 72.25, 64.80, 55.75, 41.97. HRMS (ESI): m/z calculated 460.2046 for $[C_{28}H_{29}NO_5 + H]^+$, found 460.2088.

Synthesis of 2,3,4-tri-O-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (13)

*Method 1 (from compound **12** to **13**)*: To a solution of 2,3,4-tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol-*N*-cyclic carbamate **12** (280 mg, 0.609 mmol) in MeOH (20 mL), 50% aqueous KOH (20 mL) was added. The reaction mixture was stirred for 20 hours at 80°C. Reaction progression was monitored by TLC and after disappearance of starting material; solvent was removed under reduced pressure. Water was added and the mixture was extracted with EA (3 × 50 mL). Combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography using elution gradient (SiO_2, petroleum ether/ethyl acetate 1:1, v/v) gave 13 (200 mg, 75%) as white solid.

*Method 2 (from compound **10** to **13**)*: To a solution of 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-glucitol **10** (200 mg, 0.33 mmol) in EtOH or MeOH (20 mL), 50% aqueous KOH or NaOH (20 mL) was added. The reaction mixture was stirred for 6–12 hours at 80°C. Reaction progression was monitored by TLC and after disappearance of starting material; solvent was removed under reduced pressure. Water was added and extractions were made with EA (3 × 50 mL). Combined organic layers were dried over Na_2SO_4, filtered and concentrated. Flash column chromatography using elution gradient (SiO_2, petroleum ether/ethyl acetate 1:1, v/v) gave **13** as white solid. Yield see Table 1, white solid, mp 80–85°C, $R_f = 0.16$ (petroleum ether/ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.34 (m, 15H), 5.0 (d, $J = 10$ Hz, 1H), 4.92 (d, $J = 10$ Hz, 1H), 4.87 (d, $J = 10$ Hz, 1H), 4.66–4.73 (m, 2H), 4.64 (d, $J = 10$ Hz, 1H), 3.77 (dd, $J = 8, 3$ Hz, 1H), 3.57–3.61 (m, 2H), 3.48–3.53 (m, 1H), 3.34 (t, $J = 10$ Hz, 1H), 3.26 (d, $J = 10.05, 5.0$ Hz, 1H), 2.62–2.65 (m, 1H), 2.54 (dd, $J = 10.05, 5.0$ Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.88, 137.48, 137.35, 127.56, 127.50, 127.23, 127.01, 126.94, 126.86, 126.65, 86.22, 79.54, 78.60, 76.36, 76.11; 75.85, 74.72, 74.20, 71.91, 61.78, 60.10, 47.12. HRMS (ESI): m/z calculated 434.2253 for $[C_{27}H_{31}NO_4 + H]^+$, found 434.2317.

Synthesis of 2,3,4-tri-O-benzyl-N-octyl-1,5-dideoxy-1,5-imino-D-glucitol (14)

To a solution of 2,3,4-tri-*O*-benzyl-1,5-dideoxy-1,5-imino-D-glucitol **13** (100 mg, 0.23 mmol) in MeOH and AcOH mixture (v/v 200:1, 10 mL), n-octanal (150 µl,

1.61 mmol) was added. After stirring for one hour at 60°C, $NaCNBH_3$ (80 mg, 1.15 mmol) was added and the mixture was refluxed for 18 hours at 80°C. Reaction was quenched with 1N HCl solution (100 µl) and was extracted with EA (3 × 50 mL). Combined organic layers were washed with aqueous sodium bicarbonate (50 mL) and brine (50 mL), dried (over Na_2SO_4), filtered and concentrated. Flash chromatography using gradient elution (SiO_2, petroleum ether/ethyl acetate 6:1, v/v) gave **14** (115 mg, 88%) as yellow oil. Yield 88%, yellow oil, $R_f = 0.62$ (petroleum ether/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.37 (m, 15H), 4.9 (d, $J = 11$ Hz, 1H), 4.96 (d, $J = 11$ Hz, 1H), 4.85 (d, $J = 11$ Hz, 1H), 4.72 (d, $J = 11$ Hz, 1H), 4.66–4.69 (m, 2H), 3.52–3.82 (m, 5H), 3.11 (dd, $J = 10$, 5 Hz, 1H), 2.48 (m, 1H), 2.43 (m, 1H), 2.26–2.29 (m, 1H), 2.23 (d, $J = 10$ Hz, 1H), 1.27–1.49 (m, 12H), 0.88 (t, $J = 5$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.50, 137.45, 137.40, 127.50, 127.48, 127.05, 126.94, 126.86, 126.80, 85.92, 77.38, 76.99, 76.34, 76.09, 75.83, 74.64, 74.41, 71.98, 63.77, 56.79, 51.31, 43.31, 32.29, 30.88, 28.69, 28.35, 26.79, 23.77, 21.71, 13.15. MS (ESI): m/z calculated 546.3505 for $[C_{35}H_{47}NO_4 + H]^+$, found 546.3570.

Synthesis of 6-O-ethyl-2,3,4-tri-O-benzyl-N-Octyl-1,5-dideoxy-1,5-imino-D-glucitol (15)

NaH (10 mg, 0.22 mmol) was added to the solution of 2,3,4-tri-*O*-benzyl-*N*-octyl-1,5-dideoxy-1,5-imino-D-glucitol **14** (60 mg, 0.11 mmol) in dry DMF (2 mL) at 0°C. After stirring for 30 minutes, ethyl iodide (20 µl, 0.22 mmol) was introduced and the reaction was stirred for 6 hours at room temperature. Reaction was quenched by adding water and extracted with EA (3 × 50 mL). Combined organic layers were dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography using gradient elution (SiO_2, petroleum ether/ethyl acetate 10:1, v/v) to afford **15** (50 mg, 78%) as yellow oil. Yield 78%, yellow oil, $R_f = 0.68$ (petroleum ether/ethyl acetate 6:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.35 (m, 15H), 4.92–4.96 (m, 2H), 4.83 (d, $J = 11$ Hz, 1H), 4.63–4.70 (m, 2H), 4.60 (d, $J = 11$ Hz, 1H), 3.58–3.67 (m, 4H), 3.49 (d, $J = 3.5$ Hz, 1H), 3.42–3.48 (m, 2H), 3.08 (dd, $J = 10$, 5 Hz, 1H), 2.66–2.68 (m, 2H), 2.28–2.31 (m, 1H), 2.25 (d, $J = 10$ Hz), 1.26–1.33 (m, 12H), 1.20 (t, $J = 5$ Hz, 3H), 0.89 (t, $J = 5$ Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.15, 137.80, 137.66, 127.42, 127.35, 126.88, 126.64, 126.45, 86.39, 77.81, 77.64, 74.34, 71.81, 65.59, 64.92, 54.72, 51.49, 30.88, 30.49, 29.24, 28.75, 28.58, 28.34, 26.64, 22.41,14.09, 13.16. HRMS (ESI): m/z calculated 574.3818 for $[C_{37}H_{51}NO_4 + H]^+$, found 574.3880.

Synthesis of 6-O-butyl-2,3,4-tri-O-benzyl-N-octyl-1,5-dideoxy-1,5-imino-D-glucitol (16)

Compound **16** was prepared from 2,3,4-tri-*O*-benzyl-*N*-octyl-1,5-dideoxy-1,5-imino-D-glucitol **14** (70 mg, 0.128 mmol) and n-butyl bromide (40 µl, 0.256 mmol) as described in the preparation of 6-*O*-ethyl-2,3,4-tri-*O*-benzyl-*N*-Octyl-1,5-dideoxy-1,5-imino-D-glucitol **15**, giving **16** (55 mg, 71%) as colorless oil. Yield 71%, colorless oil, $R_f = 0.26$ (petroleum ether/ethyl acetate 10:1). ^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.26–7.35 (m, 15H), 4.96–4.99 (m, 2H), 4.86 (d, $J = 10$ Hz, 1H), 4.67–4.73 (m, 2H), 4.62 (d, $J = 10$ Hz, 1H), 3.6–3.7 (m, 4H), 3.51 (d, $J = 10$ Hz, 1H), 3.46–3.48 (m, 1H), 3.37–3.39 (m, 1H), 3.11 (dd, $J = 10$, 5 Hz, 1H), 2.69–2.70 (m, 2H), 2.34 (d, $J = 10$ Hz, 1H), 2.26–2.31 (m, 1H), 1.58–1.61 (m, 2H), 1.36–1.44 (m, 4H), 1.26–1.30 (m, 10H), 0.92 (t, $J = 5$ Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.14, 137.83, 137.67, 127.45, 127.38, 126.95, 126.88, 126.67, 126.49, 86.43, 77.88, 77.66, 74.40, 74.31, 71.82, 70.30, 65.50, 62.87, 53.70, 51.52, 30.91, 30.63, 28.61, 28.37, 26.65, 21.74, 18.56, 13.20, 13.01. HRMS (ESI): m/z calculated 602.4131 for $[C_{39}H_{55}NO_4 + H]^+$, found 602.4198.

Synthesis of 6-O-ethyl-N-octyl-1,5-dideoxy-1,5-imino-D-glucitol (17)

A solution of 6-*O*-ethyl-2,3,4-tri-*O*-benzyl-*N*-Octyl-1,5-dideoxy-1,5-imino-D-glucitol **15** (80 mg, 0.132 mmol) in MeOH (8 mL) and THF (4 mL) was acidified with concentrated HCl upto pH = 2. Catalytic amount of 10% Pd/C (20 mg) was added and the mixture was stirred under H_2 atmosphere for 48 hours at room temperature. After completion of reaction as indicated by TLC, mixture was passed through a short pad of ce1lite and washed with warm MeOH and concentrated. The residue was purified by flash column chromatography using gradient elution (SiO_2, ethyl acetate/MeOH 10:1, v/v) to afford **17** (30 mg, 68%) as yellow oil. Yield 68%, yellow oil, $R_f = 0.6$ (ethyl acetate/methanol 5:1). ^{1}H NMR (500 MHz, MeOD) δ 3.72 (dd, $J = 9$ Hz, 1H), 3.64 (dd, $J = 3.5$, 10.5 Hz, 1H), 3.45–3.53 (m, 2H), 3.29 (t, $J = 10$ Hz, 1H), 3.11 (t, $J = 10$ Hz, 1H), 2.94 (dd, $J = 5$, 10 Hz, 1H), 2.72–2.77 (m, 1H), 2.52–2.58 (m, 1H), 2.19–2.22 (m, 1H), 2.16 (d, $J = 10$ Hz), 1.43–1.50 (m, 2H), 1.29–1.33 (m, 10H), 1.20 (t, $J = 5$ Hz, 3H), 0.91 (t, $J = 5$ Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 78.23, 69.85, 68.35, 66.47, 65.16, 63.81, 55.40, 51.61, 30.63, 28.38, 28.21, 28.04, 26.25, 22.62, 21.33, 13.06, 12.06. HRMS (ESI): m/z calculated 304.4430 for $[C_{16}H_{33}NO_4 + H]^+$, found 304.2459.

Synthesis of 6-O-butyl-N-octyl-1,5-dideoxy-1,5-imino-D-glucitol (18)

Compound **18** was prepared from 6-*O*-butyl-2,3,4-tri-*O*-benzyl-*N*-octyl-1,5-dideoxy-1,5-imino-D-glucitol **16** (70 mg, 0.122 mmol) as described in the preparation of 6-*O*-ethyl-*N*-octyl-1,5-dideoxy-1,5-imino-D-glucitol **17**, giving **18** (22 mg, 59%) as yellow oil. Yield 59%, yellow oil, $R_f = 0.8$ (ethyl acetate/methanol 5:1). ^{1}H NMR (500 MHz, MeOD) δ 3.69 (d, $J = 10$ Hz, 1H), 3.59 (dd, $J = 10$, 5 Hz, 1H), 3.40–3.46 (m, 2H), 3.23 (t, $J = 10$ Hz, 1H), 3.11 (t, $J = 10$ Hz, 1H), 2.95 (dd, $J = 10$, 5 Hz, 1H), 2.76 (m, 1H), 2.55 (m, 1H), 2.24 (d, $J = 5$ Hz, 1H), 2.15–2.20 (m, 1H), 1.51–1.54 (m, 2H), 1.41–1.43 (m, 2H), 1.26–1.38 (m, 12H), 0.96 (t, $J = 5$ Hz, 3H), 0.88 (t, $J = 5$ Hz, 3H); ^{13}C NMR (126 MHz, MeOD) δ 76.32, 73.17, 69.23, 67.12, 64.62, 64.16, 58.3, 55.3, 30.49, 30.39, 28.23, 27.86, 25.29, 22.02, 21.15, 18.01, 11.88, 11.72. MS (ESI): m/z calculated 349.2723 for $[C_{18}H_{37}NO_4 + NH_4]^+$, found 349.2746.

References

[1] Zhang, G.L.; Chen, C.; Xiong, Y.; Zhang, L.H.; Ye, J.; Ye, X.S. Synthesis of N-substituted iminosugar derivatives and their immunosuppressive activities. *Carbohydr. Res.* **2001**, *6*, 780–786.

[2] Tsuruoka, T.; Fukuyasu, H.; Ishii, M.; Usui, T.; Shibahara, S.; Inouye, S.J. Inhibition of mouse tumor metastasis with nojirimycin- related compounds. *Antibiot.* **1996**, *49*, 155–161.

[3] Somsák, L.; Nagya, V.; Hadady, Z.; Docsa, T.; Gergely, P. Glucose analog inhibitors of glycogen phosphorylases as potential antidiabetic agents: recent developments. *Curr. Pharm. Des.* **2003**, *9*, 1177–1189.

[4] Durantel, D.; Branzanichita, N.; Carrouéedurantel, S.; Butters, T.D.; Dwek, R.A.; Zitmann, N. Study of the mechanism of antiviral action of iminosugar derivatives against bovine viral diarrhea virus. *J. Virol.* **2001**, *75*, 8987–8998.

[5] Yu, W.; Gill, T.; Wang, L.; Du, Y.; Ye, H.; Qu, X.; Guo, J.T.; Cuconati, A.; Kang, Z.; Timothy, M.B.; Xiaodong, X.; Chang, C.J. Design, synthesis, and biological evaluation of N-Alkylated deoxynojirimycin (DNJ) derivatives for the treatment of dengue virus infection. *Med. Chem.* **2012**, *55*, 6061–6075.

[6] Mitrakou, A.; Tountas, N.; Raptis, A.E.; Bauer, R.J.; Schulz, H.; Raptis, S.A. Long-term effectiveness of a new alpha-glucosidase inhibitor (BAY m1099-miglitol) in insulin-treated type 2 diabetes mellitus. *Diab. Med.* **1998**, *15*, 657–660.

[7] Butters, T.D.; Dwek, R.A.; Platt, F.M. Inhibition of glycosphingolipid biosynthesis: application to lysosomal storage disorders. *Chem. Rev.* **2000**, *100*, 4683–4696.

[8] Butters, T.D.; Dwek, R.A.; Platt, F.M. Iminosugar inhibitors for treating the lysosomal glycosphingolipidoses. *Glycobiology* **2005**, *10*, 43R–52R.

[9] Winchester, B.G. Iminosugars: from botanical curiosities to licensed drugs. *Tetrahedron: Asymmetry* **2009**, *20*, 645–651.

[10] Cox, T.; Lachmann, R.; Hollak, C.; Aerts, J.; van Weely, S.; Hrebicek, M.; Platt, F.; Butters, T.; Dwek, R.; Moyses, C.; Gow, I.; Elstein, D.; Zimran, A. Novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. *Lancet* **2000**, *355*, 1481–1485.

[11] Cheng, W.C.; Weng, C.Y.; Yun, W.Y.; Chang, S.Y.; Lin, Y.C.; Tsai, F.J.; Huang, F.Y.; Chen, Y.R. Rapid modifications of N-substitution in iminosugars: development of new β-glucocerebrosidase inhibitors and pharmacological chaperones for Gaucher disease. *Bioorg. Med. Chem.* **2013**, *21*, 5021–5028.

[12] Barton, N.W.; Brady, R.O.; Dambrosia, J.M.; Di Bisceglie, A.M.; Doppelt, S.H.; Hill, S.C.; Mankin, H.J.; Murray, G.J.; Parker, R.I.; Argoff, C.E.; Grewal, R.P.; Yu, K.T. Replacement therapy for inherited enzyme deficiency- macrophage targeted glucocerebrosidase for Gaucher's disease. *N. Engl. J. Med.* **1991**, *324*, 1464–1470.

[13] Aerts, J.M.; Hollak, C.; Boot, R.; Groener, A. Biochemistry of glycosphingolipid storage disorders: implications for therapeutic intervention. *Philos. Trans. R. Soc. Lond., B, Biol. Sci.* **2003**, *358*, 905–914.

[14] Platt, F.M.; Neises, G.R.; Dwek, R.A.; Butters, T.D. N-butyldeoxynojirimycin is a novel inhibitor of glycolipid biosynthesis. *J. Biol. Chem.* **1994**, *269*, 8362–8365.

[15] Wennekes, T.; van den Berg, R.J.B.H.N.; Donker, W.; van der Marel, G.A.; Strijland, A.; Aerts, J.M.F.G.; Overkleeft, H.S.J. Development of adamantan-1-yl-methoxy-functionalized 1-deoxynojirimycin derivatives as selective inhibitors of glucosylceramide metabolism in man. *Org. Chem* **2007**, *72*, 1088–1097.

[16] Wennekes, T.; Meijer, A.J.; Groen, A.K.; Boot, R.G.; Groener, J.E.; van Eijk, M.; Ottenhoff, R.; Bijl, N.; Ghauharali, K.; Song, H.; O'Shea, T.J.; Liu, H.; Yew, N.; Copeland, D.; van den Berg, R.J.; van der Marel, G.A.; Overkleeft, H.S.; Aerts, J.M. Dual-action lipophilic iminosugar

improves glycemic control in obese rodents by reduction of visceral glycosphingolipids and buffering of carbohydrate assimilation. *J. Med. Chem.* **2010**, *53*, 689–698.

[17] van den Berg, R.J.B.H.N.; Wennekes, T.; Ghisaidoobe, A.; Donker-Koopman, W.E.; Strijland, A.; Boot, R.G.; van der Marel, G.A.; Aerts, J.M.F.G.; Overkleeft, H.S. Assessment of partially deoxygenated deoxynojirimycin derivatives as glucosylceramide synthase inhibitors. *ACS Med. Chem. Lett.* **2011**, *2*, 519–522.

[18] Boucheron, C.; Toumieux, S.; Compain, P.; Martin, O.R.; Ikeda, K.; Asano, N. Synthesis of 4-O-glycosylated 1-deoxynojirimycin derivatives as disaccharide mimics-based inhibitors of human β-glucocerebrosidase. *Carbohydr. Res.* **2007**, *342*, 1960–1965.

[19] Banwell, M.G.; Ma, X.; Asano, N.; Ikeda, K.; Lambert, J.N. Chemoenzymatic syntheses of (-)-1-deoxymannojirimycin (DMJ) and its naturally occurring 6-O-α-L-rhamnopyranosyl glycoside. *Org. Biomol. Chem.* **2003**, *1*, 2035–2037.

[20] Iftikhar, M.; Wang, L.; Fang, Z. Synthesis of 1-deoxynojirimycin: exploration of optimised conditions for reductive amidation and separation of epimers. *J. Chem. Res.* **2017**, *41*, 460–464.

[21] Vaughn, H.L.; Robbind, M.D. Amides are known to undergo hydrolysis when treated with aqueous sodium hydroperoxide. *J. Org. Chem.* **1975**, *40*, 1187–1189.

[22] Zhao, Z.; Song, L.; Mariano, P.S. A concise sequential photochemical-metathesis approach for the synthesis of (+)-castanospermine and possible uniflorine-A stereoisomers. *Tetrahedron* **2005**, *61*, 8888–8894.